Programs in Personalized Medicine Built on Genomics

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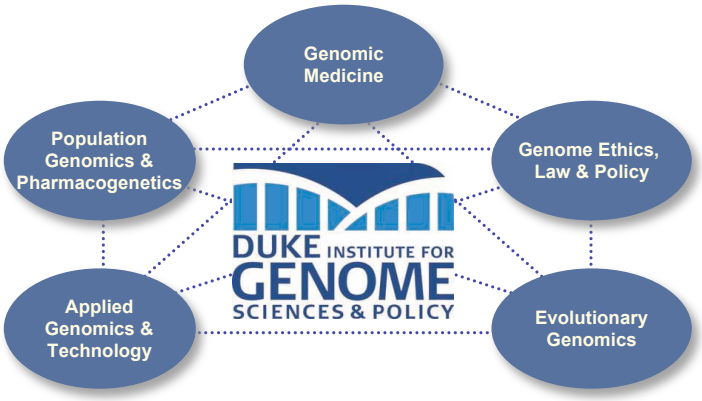
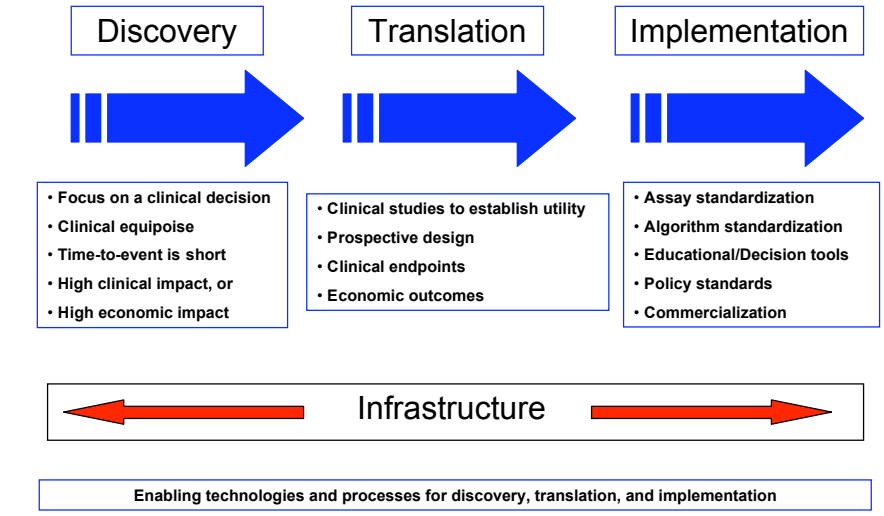


IGSP Genomic Medicine Strategy



Introduction

- Definition and Key Questions
- Drivers and examples
  - Genomic Prognosis
  - Pharmacogenomics
- Opportunities and Challenges
- "External" Forces

Personalized Medicine: Definition

"Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient's disease or predisposition toward a disease…. Personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health."

NHLBI Strategic Planning, Theme #10.

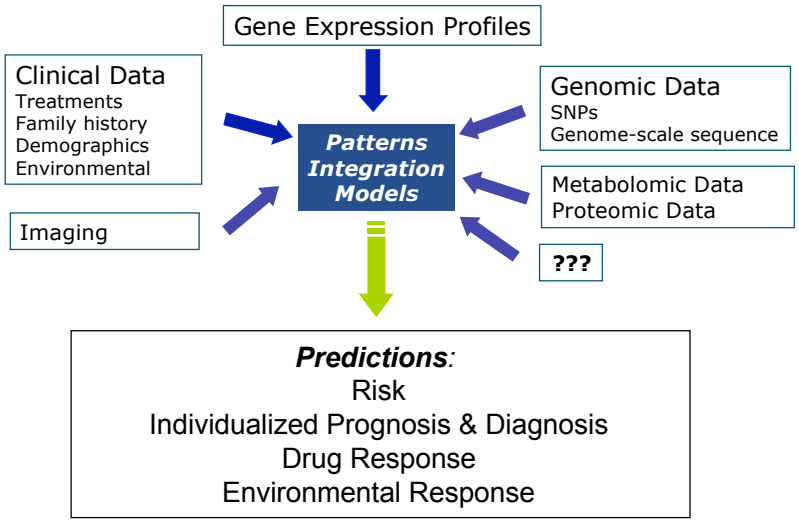
The Challenge for Personalized Treatment

- How to improve prognosis to identify the patients **Who to treat?** treatment?
- How to identify more effective therapeutic opportun**How to treat?**e individual patient?

A New Biomarker Toolbox

Human Genome Sequence	**Single nucleotide polymorphisms (SNPs); ~ 10,000,000**
Gene Expression Profiles	**Microarrays of ~25,000 gene transcripts**
Proteome	**Protein arrays of specific protein products; ~ 100,000**
Metabolome	**Small molecule metabolites; ~ 5000**

New Predictive Models of Outcome



Genetic Loci That Predict Complex Disease

Myocardial Infarction

- Myocyte Enhancer Factor 2A (MEF2A)
- 5-lipoxygenase activating protein (FLAP)
- GATA-2

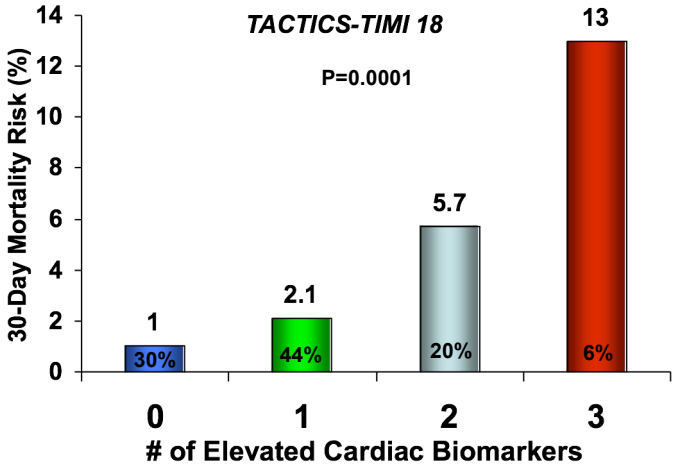
Cancer

- BRCA-1/2
- APC

Genome Wide Association Studies

- NHLBI RFA funded now
  NHGRI, NIEHS, NCI, NIGMS are participants
- Genome Wide Association Studies in the HapMap era
  - Identify an optimum set of 300,000 tag SNPs
  - Collect 1000 cases and 1000 controls
  - Genotype all DNAs for all SNPs
  - 600 million – not 20 billion - genotypes
  - @ $0.005/genotype = ~ $3 million for each disease

Multi-marker Approach: cTnI, CRP, & BNP



Sabatine et al. Circulation 2002; 105: 1760.

Proteomic Biosignatures in Acute Coronary Syndromes

Inflammation/ Plaque Stability

- CRP
- IL-6
- IL-10
- IL-18
- Pregnancy associated plasma protein-A
- CD40 ligand
- Myeloperoxidase
- Placental Growth Factor
- Vascular Endothelial Growth Factor
- Fibrinogen
- Serum Amyloid A
- Monocyte Chemoattractant Protein-1

Ischemia

- Unbound Free Fatty Acids
- Ischemia Modified Albumin
- Whole Blood Choline
- B-type natruiretic peptide

Thrombosis

- Plasminogen Activator Inhibitor -1
- CD40 ligand
- Von Willibrand Factor
- D dimer

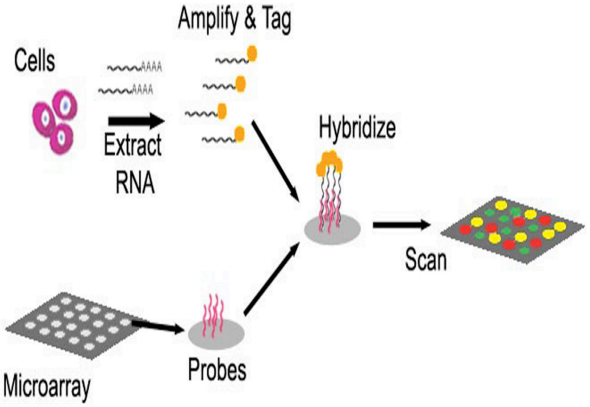
Remodeling CHF

- B-type Natruiretic Peptide
- Matrix Metalloproteases

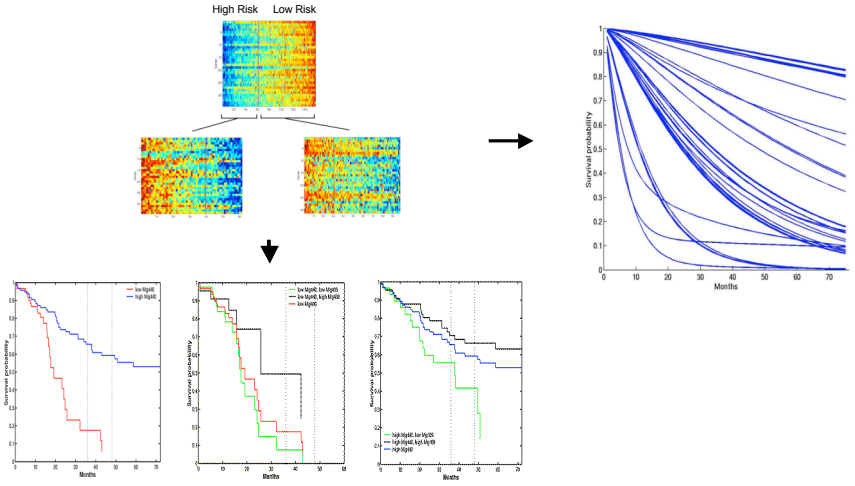
Necrosis

- Troponin I/T
- Creatine Kinase - MB
- Myoglobin

RNA: Gene Expression Profiling

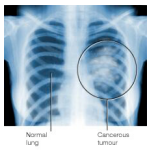


Genomic Analyses Can Refine Prognosis



An Opportunity in Lung Cancer

Early Stage NSCLC Treatment Protocol



Diagnosis

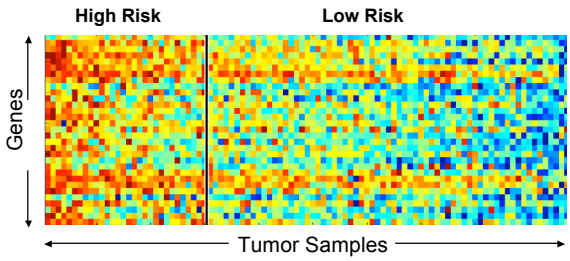
Tumor is resected and measured

Stage 1a: Observation

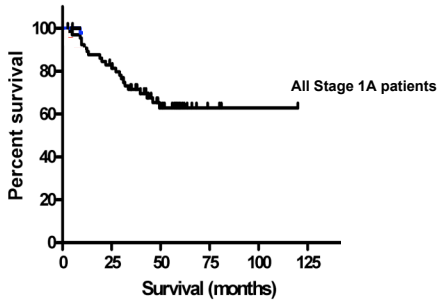
Stage 1b-3: Adjuvant Therapy

Yet, 30% of Stage 1A patients will recur and die - how to identify these individuals?

A Genomic Pattern That Predicts Recurrence



Identification of Stage 1A Patients at Increased Risk



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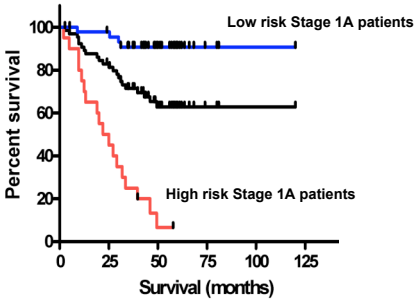
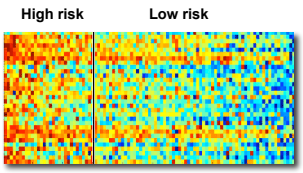
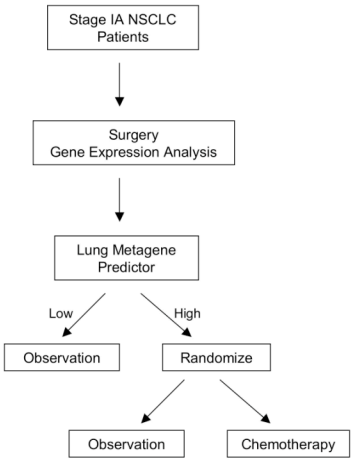




Potti et al, NEJM, 2006

A Duke-Led Study to Select Lung Cancer Patients for Treatment



After Prognosis, How Best to Treat?

Standard-of-Care

- Cisplatin/paclitaxel
- Cisplatin/gemcitabine
- Cisplatin/docetaxel
- Cisplatin/vinorelbine

Only 1/5 patients will respond

The rest are treated ineffectively

How to choose the right therapy for the individual patient?

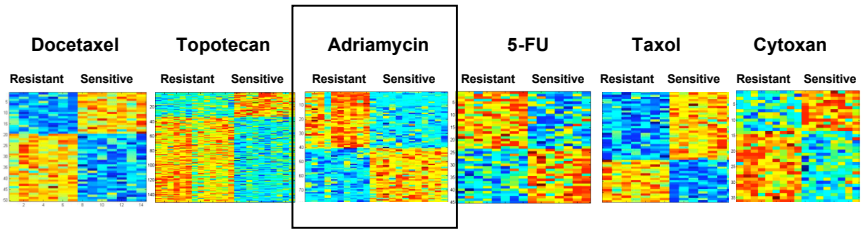
Herceptin - The Importance of Patient Selection

All Breast Cancer Patients → Herceptin → < 10% Response

Her2+ Breast Cancer Patients → Herceptin → 35-50% Response

Can we do the same for commonly used chemotherapies?

A Panel of Predictors for Cytotoxic Chemotherapies

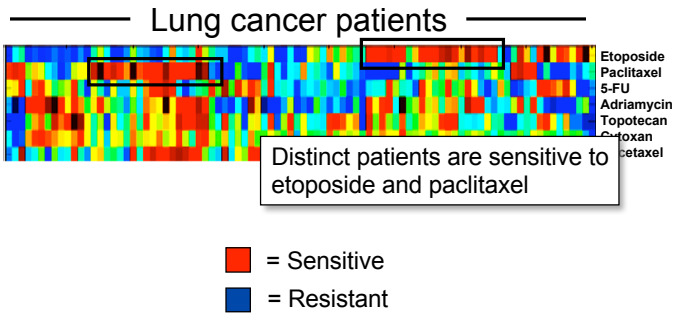


Potti et al, Nature Medicine, 2006

A Tool to Guide the Use of Chemotherapies

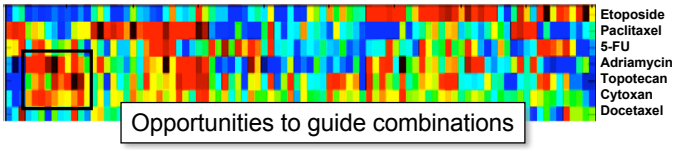
All CML Patients	Genomic-Selected CML Patients
↓	↓
Adriamycin	Adriamycin
↓	↓
17% Response	57% Response

Patterns of Predicted Sensitivity to Cytotoxic Chemotherapies



Patterns of Predicted Sensitivity to Cytotoxic Chemotherapies

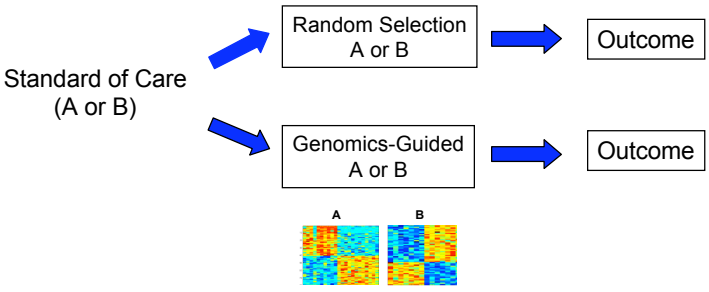
Lung cancer patients



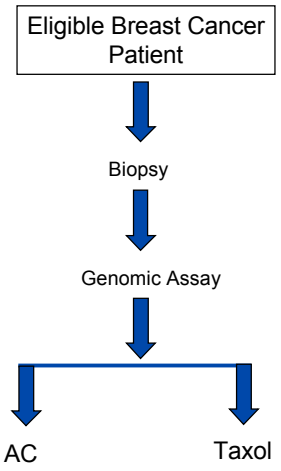
= Sensitive

= Resistant

An Opportunity to Guide Therapy



Putting Personalized Cancer Treatment to Practice at Duke



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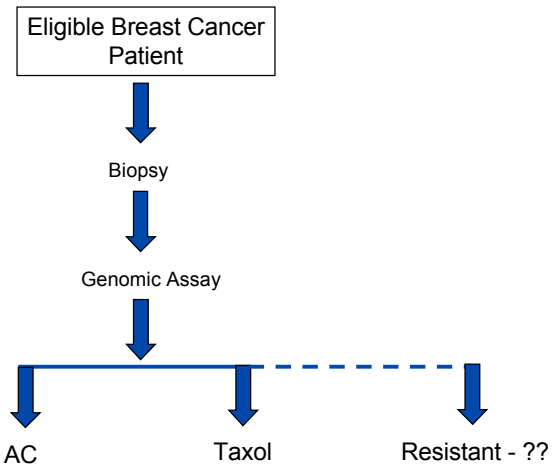

An Array of Targeted Therapies

Drug	Target	Status
Anastrozole	**ER**	Approved for ER positive breast cancer
Bevacizumab	**VEGF/VEGF-R**	Approved for metastatic colorectal cancer in combination with 5-FU
Bortezomib		Approved for advanced multiple myeloma
Cetuximab	**EGFR**	Approved for advanced head and neck cancer
Erlotinib	**EGFR**	Approved for advanced NSCLC
Exemestane	**ER**	Approved for ER positive breast cancer
Imatinib mesylate	**BCR-ABL**	Approved for chronic myelogenous leukemia
Sorafenib	**Raf, VEGF, Kit, FLT3**	Approved for advanced renal cell carcinoma
Tamoxifen	**ER**	Approved for ER positive breast cancer
Trastuzumab	**Her2**	Approved for Her2 positive breast cancer
AMN 107	**BCR-ABL, KIT, PDGFR**	Phase II
Roscovitine	**Cdk (E2F)**	Phase II
Gefitinib	**EGFR**	Phase III
ABX-EGF	**EGFR**	Phase III
GW-572016	**EGFR, Her2**	Phase III
BMS-214662 (FTI)	**Ras**	Phase I/II
Tipifarnib (FTI)	**Ras**	Phase II
Everolimus	**mTOR**	Phase II
Temsirolimus	**mTOR**	Phase II
Ly294002	**PI3K**	Phase I/II
FTS	**Ras**	Phase I/II
ZD6474	**RET, VEGF**	Phase II/III
SU6656	**Src**	Phase I/II
AZD0530	**Src**	Phase II
BMS-384825	**Src, BCR-ABL, KIT**	Phase III
SU11248	**VEGF, RET, FLT3**	Phase III
PTK787/zk	**VEGFR-1, VEGFR-2**	Phase III

Signaling Pathways Underlying the Oncogenic Phenotype

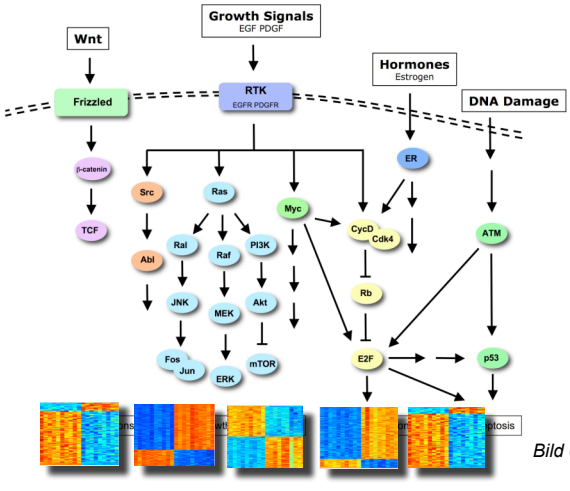

Bild et al, Nature, 2006

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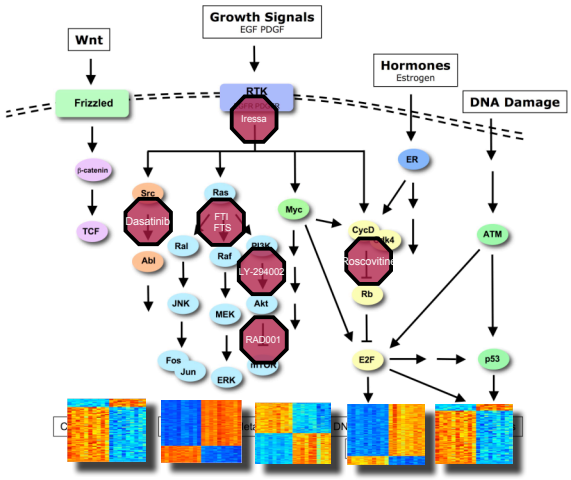


Putting Personalized Medicine to Practice at Duke

Eligible Lung Cancer Patient

⇩

Biopsy

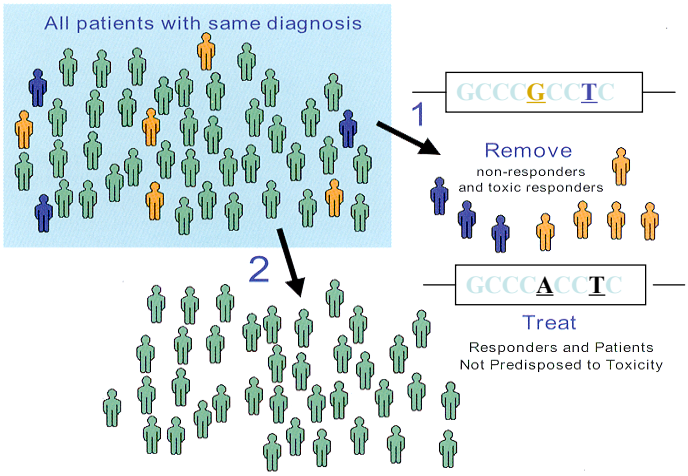
⇩

Pathway Assay

⇩

Dasatinib (Src inhibitor)

Pharmacogenetics Applied to the Practice of Medicine



From McLeod and Evans, Ann Rev of Pharmacol and Toxicol, 2001: 41,101-121

The Need for Tailored Therapy in Cardiovascular Medicine

Event Rates (%)

Trial	N	Drug	Placebo	Treated	Benefit	Lack of Benefit
HOPE	9451	Ramipril	17.8	14.0	3.8	96.2
APTC	5435	Aspirin	14.0	10.0	4.0	96.0
FTT	58600	Lytics	11.5	9.6	1.9	98.1
4S	4444	Simvastatin	28.0	19.0	9.0	91.0
EPIC	2099	Abciximab	12.8	8.3	4.5	95.5
CURE	12502	Clopidogrel	11.5	9.3	2.2	97.8

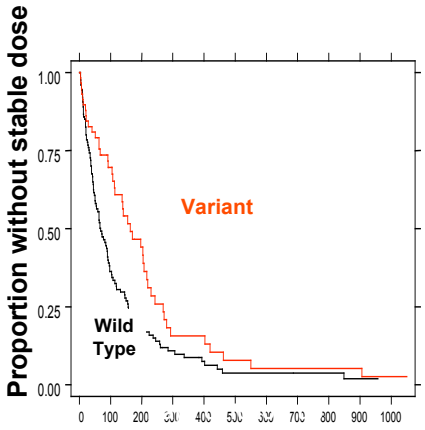
Mukherjee and Topol, Prog Card Dis 44:479-98, 2002

Logic of pharmacogenetics

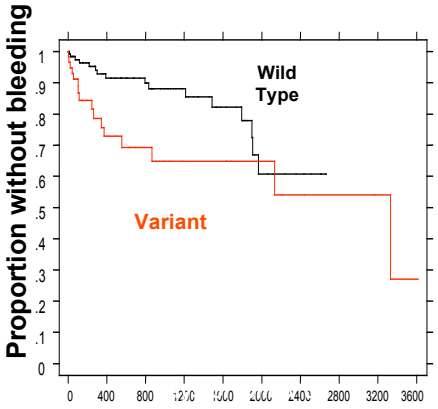
- Variation in response
- Recent epidemic of licit drug use with US sales of greater than $250 billion
- 100,000 patients die annually due to ‘adverse drug reactions’ (ADRs)
- 2 million hospitalizations annually due to ADRs
- Top 10 cause of death
- $100+ billion annual economic impact

JAMA 1998

PGx and Drug Safety: CYP2C9 Variants and Outcomes to Warfarin Therapy for Anticoagulation



Time to Stable Dosing

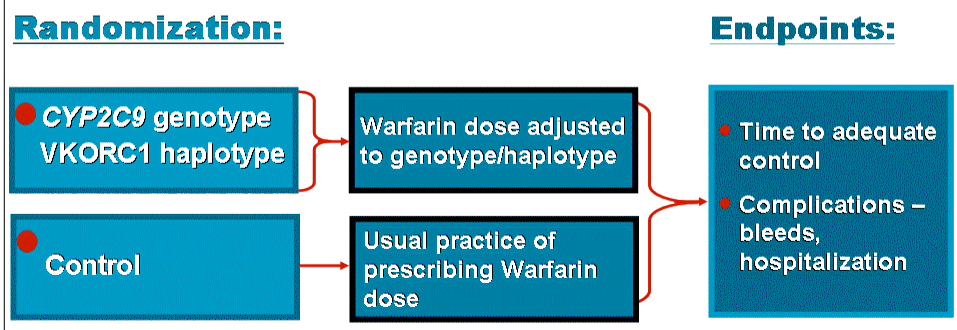


Time to Life Threatening Bleeds

Higashi 2002

Gene-Based Clinical Trial

Warfarin Resistance and Sensitivity



Opportunities in Medicine

- Genetics → Susceptibility; Drug response
- Genomics → Classifiers; Prognosis; Monitoring; Drug response
- Imaging → Monitoring; Prognosis

Pharmacogenomics: Suggested standards

- Clear definition of phenotypes
- Pathway-based candidate genes
- Replication of findings (validation)
- Prospective evaluation

Need AC. Nat Genet 2005; 37: 671-81.

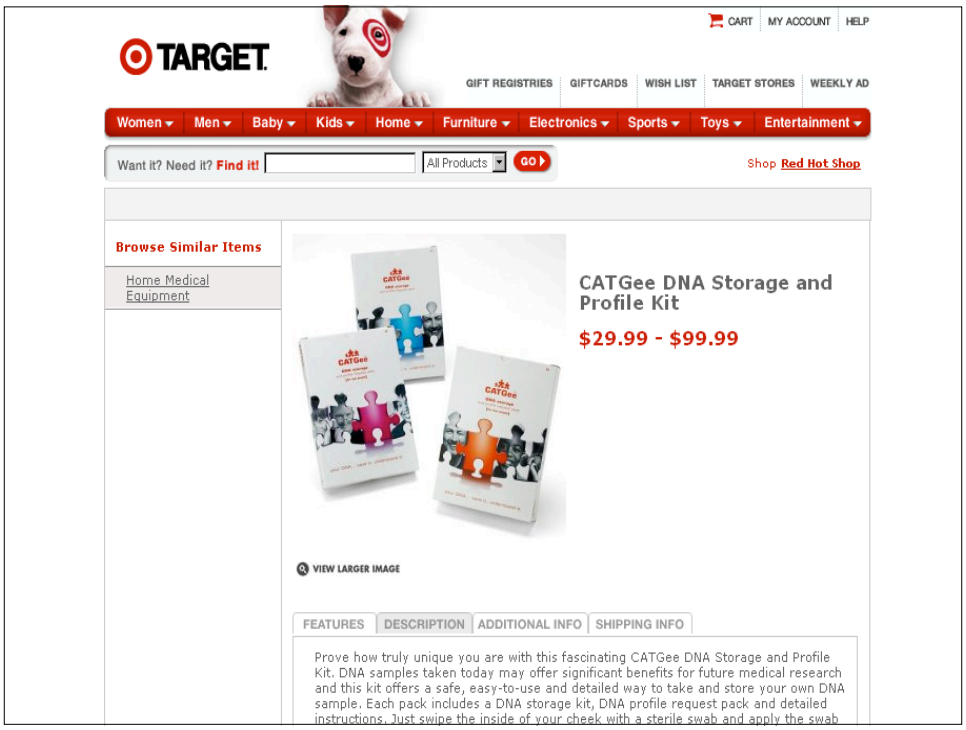
What's Needed:

- Comprehensive biobanks/registries
- Accessible tools
- Novel statistical approaches
- Novel partnerships with industry
- Train the next generation
- Support teams vs. individuals

NHLBI Strategic Planning, Theme #10.

External Forces

- FDA
  - Critical Path Initiative 2004
  - Pharmacogenomic Guidance 2004
  - In Vitro Diagnostic Multivariate Index Assays *Draft* Guidance 2006
- Obama
  - **Genomics and Personalized Medicine Act of 2006**
  - "To improve access to and appropriate utilization of valid, reliable and accurate molecular genetic tests by all populations thus helping to secure the promise of personalized medicine to all Americans"



Personalized Medicine and Policy Issues

- The Test and the Test *Result*
- Reimbursement
- Privacy
- Discrimination
- Direct to Consumer
- Education

NIH…Personalized

We look to a future in which medicine will be predictive, preventive, preemptive and personalized.

The Team

- Andrea Bild
- Tom Burke
- Mike Datto
- Holly Dressman
- Susanne Haga
- David Harpole
- Joe Nevins
- Anil Potti
- Hunt Willard